

# Class Review: Oral Inhaled Corticosteroids

## Factors Affecting Feasibility of Closing the Oral Inhaled Corticosteroid Class on the Department of Defense Basic Core Formulary

Prepared by the Department of Defense (DoD) Pharmacoeconomic Center (PEC) for the 15 Nov 00 meeting of the DoD Pharmacy & Therapeutics (P&T) Executive Council. Minutes of DoD P&T Executive Council and DoD P&T Committee meetings are available on the PEC website at [www.pec.ha.osd.mil](http://www.pec.ha.osd.mil).

### Background

- There are five oral inhaled corticosteroid products currently marketed in the U.S. One of these, triamcinolone (Azmacort; Aventis), is currently on the Department of Defense (DoD) Basic Core Formulary (BCF).
- There have been several BCF decisions made in this category over the last 3 years. A chronology is included:
  - 1997 – Budesonide, fluticasone, beclomethasone, and triamcinolone added to the BCF, flunisolide deleted.
  - Nov 1998 – Budesonide and fluticasone removed from BCF, due to MTF concerns about acquisition costs.
  - Feb 1999 – In response to triamcinolone price increase from \$5.40 to \$12.90, DOD P&T Committee decided to re-evaluate the status of triamcinolone on the BCF. Shortly thereafter, the price was reduced to \$9.60, and triamcinolone remained on the BCF.
  - Nov 1999 – In response to beclomethasone price increase from \$5.75 to \$19.27, beclomethasone was removed from the BCF.
- There is clinical evidence that oral inhaled corticosteroids improve asthma management and reduce inflammation in the airways and also lower the rate of hospitalization in asthmatics. The response to inhaled glucocorticoids is dependent upon the time of onset of steroid treatment relative to the onset of asthma symptoms, with earlier use yielding better results. For this reason, all the major practice guidelines directed towards the treatment of asthma recommend daily oral inhaled corticosteroid use for all but mild asthma cases.

### Objective

- To provide information that will help the DoD P&T Executive Council evaluate the interchangeability of inhaled corticosteroids and determine the feasibility of closing the class on the BCF.

### Methods

- This document presents an overview of available evidence concerning the safety, tolerability, and efficacy of the available oral inhaled corticosteroids, as well as other factors that may affect the committee decision. Examples of other factors to be considered are: provider preference/expert opinion, current usage, compliance/convenience issues, and patent expiration considerations.

## Executive Summary

### Safety

- The inhaled corticosteroids are relatively safe agents with few serious adverse effects.
- There are no data to support significant differences between oral inhaled corticosteroids with regard to immunosuppression, ocular effects, bone metabolism, or drug-drug interactions.
- Two studies show fluticasone to have less adverse effect on height velocity than beclomethasone, and one study showed fluticasone caused less reduction in height velocity than budesonide. However, caution should be used in interpreting the data because of small sample sizes, short study duration, and/or the questionable accuracy of measuring very small changes in growth velocity.
- Several studies have shown that high-dose inhaled glucocorticoids can be absorbed systemically and cause suppression of the hypothalamic-pituitary axis with a resulting decrease in endogenous adreno-cortical activity. One meta-analysis of 34 studies showed that adrenal suppression was more likely to be seen with fluticasone than with beclomethasone, triamcinolone, or budesonide. However, none of the studies in this meta-analysis estimated HPA suppression by measuring response to ACTH, which is considered to be the best clinical indicator of this effect.

**PEC Conclusion: There is insufficient evidence to conclude that any of these agents is superior to the others in terms of safety.**

### Tolerability

- The inhaled corticosteroids are relatively well tolerated.
- Cough and oral candidiasis have been reported with the inhaled corticosteroids. Differences in the relative incidences of these adverse events are difficult to ascertain due to the nature of the data available for interpretation.
- Taste is an important tolerability issue with flunisolide.

**PEC Conclusion: There is insufficient evidence to conclude that oral inhaled corticosteroids significantly differ in their propensity to cause cough or oral candidiasis. Flunisolide has the disadvantage of extremely bitter taste.**

### Efficacy

- The evidence suggests that high potency oral inhaled corticosteroids are more efficacious than low potency for the maintenance treatment of asthma when given in comparable doses.
- Fluticasone, budesonide, and the QVar brand of beclomethasone are all FDA approved for reduction of oral systemic steroid dose in asthma and appear to be similar in efficacy at comparable doses.

#### PEC Conclusion

- **Evidence suggests that high potency oral inhaled corticosteroids are more efficacious than low potency for the maintenance treatment of asthma when given in comparable doses. Fluticasone, budesonide, and QVar appear equally efficacious for reducing the required dose of oral systemic steroids.**

### Other Factors

- The patent for beclomethasone expired December 15, 1999. However, multiple generics have not entered the market due to the difficulty in producing this drug/dosage form. The FDA recently approved QVar® (beclomethasone 40 and 80 mcg, 3M Pharmaceuticals), a branded, non-AB rated generic product. The next corticosteroid compound patent expiration will be fluticasone, on November 14, 2003.
- Published national CPGs recommend early treatment with oral inhaled corticosteroids for all patients with asthma rated as moderately severe or greater. However, they do not recommend any one product over the others.

- Most providers had no strong preferences among oral inhaled corticosteroids. Those expressing a preference most commonly mentioned fluticasone for high potency. Most providers preferred to have at least one high potency and one low potency agent available. No provider recommended that this class be closed, a few specifically recommended not closing it.
- Oral inhaled corticosteroids are available in two different delivery systems, metered dose inhalers (MDIs) and dry powder inhalers (DPIs). These delivery systems deliver different amounts of drug to the lungs depending on user technique, raising concerns about switching patients from one delivery system to the other. Significant patient education might be necessary if the class was closed and patients were required to switch from an MDI to a DPI.
- Patient compliance is a major concern with these agents, and is affected by the number of puffs required to deliver the prescribed dose and the number of doses required per day. The high potency steroids (fluticasone and budesonide) have the advantage of requiring fewer puffs to deliver the required dose. While none of the oral corticosteroid inhalers are FDA labeled as once daily products, there are published studies that support the effectiveness of once daily dosing in all of the oral inhaled corticosteroids except triamcinolone.
- All of the oral inhaled corticosteroids have been used in pediatric patients. Beclomethasone and fluticasone have the bulk of the clinical trial evidence for use in pediatrics. Only beclomethasone has clinical trials to support its use in neonates and very young infants.
- Fluticasone's market share increased from 2% to 43% between 10/97 and 8/00. Over the same time period triamcinolone and beclomethasone have decreased substantially.

**PEC Conclusion: No provider recommended that this class be closed, a few specifically recommended not closing it. Significant patient education might be necessary if the class was closed and patients were required to switch from an MDI to a DPI. From a patient compliance standpoint, the high potency steroids (fluticasone and budesonide) have the advantage of requiring fewer puffs to deliver the required dose. All oral inhaled corticosteroids have evidence that support their effectiveness of once daily dosing with the exception of triamcinolone. Beclomethasone and fluticasone have the bulk of the clinical trial evidence for use in pediatrics. Fluticasone's market share is increasing significantly relative to triamcinolone and beclomethasone.**

## Background

There are currently nine oral inhaled corticosteroid products available in the United States, representing five generic chemical entities.

**Table 1: Currently Available Oral Inhaled Corticosteroids**

Generic Name	Trade Name	Manufacturer	Dosage Form	Potency	Comments
Beclomethasone	Vanceril Beclovent	Schering Glaxo- Wellcome	MDI	Low	
Beclomethasone	Qvar	3M	MDI, CFC Free	Low	<u>Not</u> AB rated to Vanceril, Beclovent
Flunisolide	Aerobid Aerobid-M	Forest	MDI MDI with menthol	Low	
Triamcinolone	Azmacort	Rhone-Poulenc Rorer	MDI	Low	Built-in spacer
Budesonide	Pulmicort	Astra	DPI	High	
Fluticasone	Flovent Flovent Rotadisk	Glaxo- Wellcome	MDI DPI	High	Clinically, possesses attributes of both high and low potency. 44 mcg MDI and 50 mcg DPI are considered low potency. 220 mcg MDI and 250 mcg DPI are considered high potency. 110 mcg MDI and 100 mcg DPI are intermediate.

MDI=metered dose inhaler, CFC = chlorofluorocarbon, DPI= dry powder inhaler

Table 1 places the agents into two groups: high potency and low potency. Potency may be defined from two perspectives - biochemical and clinical. From a biochemical perspective, potency is defined as the relative binding affinity of the drug for corticosteroid receptors, as determined by the McKenzie skin blanching test. The reference standard for this in-vitro test is dexamethasone and it is given a value of 1, with the test drug's binding affinity reported relative to dexamethasone. While different laboratories may report a slightly different ranking, the rank order (flunisolide = triamcinolone acetate < beclomethasone dipropionate < budesonide < fluticasone propionate) has been consistent across laboratories.<sup>1</sup>

It has been argued that in-vitro potencies are not as important as those seen clinically in the patient when the drug is given. From a clinical perspective, potency is determined by a number of factors, including the amount of drug expected to reach the target cells in the lung and the pharmacokinetics of the drug at the site of activity. Hence, while fluticasone is considered to be high potency *in-vitro*, the 44 mcg MDI and 50 mcg DPI can be clinically substituted in patients requiring a lower dose of an inhaled corticosteroid. Comparative dosages based on clinical considerations are shown in Table 2.

**Table 2. Estimated Comparative Daily Dosages for Inhaled Corticosteroids in Adults and Children<sup>2</sup>**

<b>Adults and adolescents &gt; 12 years of age</b>			
<b>Drug</b>	<b>Low-Dose</b>	<b>Medium-Dose</b>	<b>High-Dose</b>
<b>Beclomethasone dipropionate</b> 42 mcg/puff (MDI) - Vanceril, Beclovent 84 mcg/puff (MDI) - Vanceril DS 40 mcg/puff (MDI) – QVar 80 mcg/puff (MDI) – QVar	<b>168 - 504 mcg</b> 4 - 12 puffs 2 - 6 puffs	<b>504 - 840 mcg</b> 12 - 20 puffs 6 - 10 puffs	<b>&gt; 840 mcg</b> > 20 puffs > 10 puffs
<b>Budesonide</b> - Pulmicort Turbuhaler 200 mcg/inhalation (DPI)	<b>200 - 400 mcg</b> 1 - 2 inhalations	<b>400 - 600 mcg</b> 2 - 3 inhalations	<b>&gt; 600 mcg</b> > 3 inhalations
<b>Flunisolide</b> - Aerobid, Aerobid-M 250 mcg/puff (MDI)	<b>500 - 1000 mcg</b> 2 - 4 puffs	<b>1000 - 2000 mcg</b> 4 - 8 puffs	<b>&gt; 2000 mcg</b> > 8 puffs
<b>Fluticasone</b> - Flovent, Flovent Rotahaler (MDI): 44, 110, 220 mcg/puff (DPI): 50, 100, 250 mcg/inhalation	<b>88 - 264 mcg</b>	<b>264 - 660 mcg</b>	<b>&gt; 660 mcg</b>
<b>Triamcinolone acetonide*</b> - Azmacort 100 mcg/puff (MDI)	<b>400 - 1000 mcg</b> 4 - 10 puffs	<b>1000 - 2000 mcg</b> 10 - 20 puffs	<b>&gt; 2000 mcg</b> > 20 puffs
<b>Children &gt; 6 years of age</b>			
<b>Drug</b>	<b>Low-Dose</b>	<b>Medium-Dose</b>	<b>High-Dose</b>
<b>Beclomethasone dipropionate</b> 42 mcg/puff (MDI) - Vanceril, Beclovent 84 mcg/puff (MDI) - Vanceril DS	<b>84 - 336 mcg</b> 2 - 8 puffs 1 - 4 puffs	<b>336 - 672 mcg</b> 8 - 16 puffs 4 - 8 puffs	<b>&gt; 672 mcg</b> > 16 puffs > 8 puffs
<b>Budesonide</b> - Pulmicort Turbuhaler 200 mcg/inhalation (DPI)	<b>100 - 200 mcg</b> 1 inhalation	<b>400 - 600 mcg</b> 1 - 2 inhalations	<b>&gt; 600 mcg</b> > 2 inhalations
<b>Flunisolide</b> - Aerobid, Aerobid-M 250 mcg/puff (MDI)	<b>500 - 750 mcg</b> 2 - 3 puffs	<b>750 - 1250 mcg</b> 4 - 5 puffs	<b>&gt; 1250 mcg</b> > 5 puffs
<b>Fluticasone</b> - Flovent, Flovent Rotahaler (MDI): 44, 110, 220 mcg/puff (DPI): 50, 100, 250 mcg/inhalation	<b>88 - 176 mcg</b>	<b>176 - 440 mcg</b>	<b>&gt; 440 mcg</b>
<b>Triamcinolone acetonide*</b> - Azmacort 100 mcg/puff (MDI)	<b>400 - 800 mcg</b> 4 - 8 puffs	<b>800 - 1200 mcg</b> 8 - 12 puffs	<b>&gt; 1200 mcg</b> > 12 puffs

MDI = metered dose inhaler; DPI = dry powder inhaler

\* Basic Core Formulary item

## Pharmacology

The precise mechanism of corticosteroid actions in inflammation in asthma is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g. mast cells, neutrophils, macrophages, and lymphocytes) and mediators (e.g. histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

The pharmacokinetics of inhaled corticosteroids is important in determining the amount of oral inhaled corticosteroid deposited in lung tissue, as well as the fraction of inhaled steroid that reaches the systemic circulation and contributes to side effects. These parameters are listed in table 8. The fraction of drug that reaches the systemic system is derived from the fraction that is absorbed and the amount that is deposited in the oropharynx and swallowed. These fractions are themselves dependent on the characteristics of the drug and the delivery system. Oropharyngeal deposition can be markedly reduced by the use of a large volume spacer or by the use of a dry powder inhaler.<sup>3,35</sup> Inhaled corticosteroid dosages of greater than the equivalent of beclomethasone 800 mcg per day have been shown to markedly increase the risk of systemic absorption.<sup>3</sup>

While the high potency formulations do not cross into the systemic circulation more readily, their high potency make it easier to deliver excessive dosages with fewer inhalations.

Most of the oral inhaled corticosteroids have active metabolites. Only beclomethasone 17-mono-propionate contributes significantly to the activity of its parent compound.

## Pharmacokinetics

**Table 3: Pharmacokinetic Characteristics of oral inhaled corticosteroids<sup>a</sup>**

Drug	Receptor Binding Affinity <sup>b</sup>	Absorption (systemic bioavailability)	Distribution (VD, Protein Binding)	Active Metabolite	Metabolism Site	Excretion (Site, T <sub>1/2</sub> )
Beclomethasone	0.4 <sup>c</sup>	~ 20% <sup>d</sup>	NA 87%	Beclomethasone 17-mono-propionate	Lung, liver	Feces, urine (<10%) 0.5 hr
Budesonide	9.4	39%	301L 85-95%	(<1%)	Liver (CYP3A)	Urine (60%), feces 2-3 hr
Flunisolide	1.8	40%	125L NA	6 b-OH (low steroid potency)	Liver	Renal (50%), feces (40%) 1.8 hr
Fluticasone	18	30% (aerosol)	258L 91%	17 b-carboxylic acid (negligible)	Liver (CYP3A)	Feces, urine (<5%) ~ 7.8hr
Triamcinolone	3.6	25%	99.5L 68%	6 b-hydroxy; 21-carboxy (< parent)	Liver, kidneys	Urine (40%) Feces (60%) 88 min

a Table adapted from Drug Facts & Comparisons, oral inhaled corticosteroid review.

b Binding affinity to human glucocorticoid receptors in vitro; relative to dexamethasone

c Beclomethasone dipropionate is converted in the liver to the more active beclomethasone monopropionate with a relative binding affinity of 13.5

d Theoretical estimate

## Safety

### Rare but Serious Side Effects

Due to the relatively small numbers of patients in clinical trials experiencing rare but serious side effects and the voluntary nature of the post-marketing adverse event reporting system, it is not possible to determine if there is a statistically or clinically significant difference among drugs with regard to the following rare but serious side effect.

- *Immunosuppression* – Oral systemic steroids have been associated with immunosuppression with resulting disseminated varicella infection in children. Some researchers have hypothesized that the effect may be similar with inhaled corticosteroids.<sup>3,4</sup> There have been case reports of at least three pediatric patients developing severe varicella infections after being placed on inhaled corticosteroids.<sup>5,6</sup>

### Other Adverse Drug Reactions

- *Ocular effects* – Studies have linked the use of oral inhaled corticosteroids to ocular effects, including glaucoma and cataracts. A 1997 case-control study demonstrated an increased risk (OR = 1.44) for ocular hypertension (glaucoma) in patients ≥ 66 y/o.<sup>7</sup> A cross-sectional study of 3654 patients showed a higher prevalence of nuclear and sub capsular cataracts (relative prevalence = 1.5, 1.9 respectively) in patients 49 – 97 y/o.<sup>8</sup> The significance of these findings in younger patients is unknown, and while beclomethasone was the only inhaled corticosteroid with long-term data, the researchers concluded that the ocular effects were likely to be a class effect and will be seen when long-term data is available on the other inhaled corticosteroids.
- *Growth suppression* – Studies have demonstrated that inhaled corticosteroids cause growth suppression in children.<sup>9,10</sup> These studies show that the risk for decreased bone growth velocity in children significantly increases as the daily dose of corticosteroid moves above the equivalent of beclomethasone 800 mcg/day. A summary of the head to head studies is shown in Table 4 below.

**Table 4. Findings from head-to-head studies on bone growth suppression from inhaled corticosteroids**

Study	Design	Treatment Groups	Results	Comments
Agertoft and Pedersen, 1994 <sup>11</sup>  Outcome measure = Height velocity and height SDS	Prospective cohort, parallel group, open; Mean age 6.2y (range 3-11y) n=62; 6 year study duration	Budesonide 43 -71 mcg/day MDI with spacer vs. DPI; dose tapering for 3-7y after initial 1-2y run-in without steroid	No significant effect of budesonide vs. run-in or controls	Study designed to determine if there is a difference between MDI and DPI.
Wolthers and Pedersen, 1993 <sup>12</sup>  Outcome measure = Height velocity	Randomized, DB, CO; n=19; 11 week study.	Fluticasone 200 mcg vs. beclomethasone 400 or 800 mcg daily	Significant reduction in height velocity with beclomethasone vs. fluticasone.	Mean growth velocities during treatment with fluticasone propionate and low and high doses of beclomethasone dipropionate were 0.34, 0.09, and 0.06 mm/week respectively.  <b>Notes:</b> Medium dose fluticasone was compared to medium/high dose beclomethasone (comparative daily dosages for children > 6 years of age).  Also, the accuracy of such small growth velocity measurements is questionable.
Rao et al, 1993 <sup>13</sup>  Outcome measure = Height velocity	Randomized, DB; n=23; 20 month study.	Fluticasone 200 mcg vs. beclomethasone 400 mcg daily	Significant reduction in height velocity with beclomethasone vs. fluticasone.	A significant difference in growth rates was found between the groups, with a slower rate of growth towards the end of the observation period in the BDP group.
Agertoft and Pedersen, 1997 <sup>14</sup>  Outcome measure = Height velocity	Randomized, DB, CO; Mean age = 9y (range= 6-12); n=48; 2 week study.	Budesonide 200 or 400 mcg, vs. Fluticasone 200 or 800 mcg daily vs. placebo	Budesonide significant reduction from placebo at 400 mcg, Fluticasone non-significant at all doses.	

DB = double blind; CO = crossover design; MDI = metered dose inhaler; DPI = dry powder inhaler; BDP= beclomethasone dipropionate.

- **HPA suppression** – Studies have demonstrated that inhaled corticosteroids cause hypothalamic-pituitary axis (HPA) suppression. A meta-analysis of 21 studies of urinary cortisol concentrations and 13 studies of morning plasma cortisol concentrations found evidence of HPA suppression that was common in the presence of higher doses of inhaled glucocorticoid therapy. This meta-analysis also concluded that fluticasone was more likely to cause greater HPA suppression than beclomethasone, budesonide, and triamcinolone particularly at doses of greater than 800 mcg/day.<sup>15</sup> Because there is high inter-patient variability in actual clinical practice, the study also concluded that the clinical significance of these findings is unknown. It is important to note that none of the studies in this meta-analysis looked at response to ACTH stimulation, which is considered to be the most accurate marker of clinical HPA suppression.
- **Bone metabolism** – One study has demonstrated that long-term use of inhaled corticosteroids has an effect on bone mineral density in a cumulative dose-dependent manner.<sup>16</sup> It is likely that the effect is similar among all of the inhaled corticosteroids. However 80% of the patients in this study received inhaled beclomethasone, so the researchers were not able to evaluate the effects of other inhaled corticosteroid products on bone metabolism.

## Special Populations

- *Pregnancy* - All oral inhaled corticosteroids are Pregnancy Category C.<sup>1</sup> They have been found to be teratogenic in rodent species. There are no well-controlled studies in pregnant women. Oral inhaled corticosteroids should be avoided in pregnancy, if possible.
- *Children* – With the exception of Flovent Rotadisc® (fluticasone), none of the oral inhaled corticosteroids are FDA approved for use in children under 6 years old. The Rotadisc® product is approved for use in children as young as 4 years old.

## Drug Interactions

There are few labeled drug-drug interactions with any of the oral inhaled corticosteroids. Ketoconazole, a potent inhibitor of cytochrome P450 3A4, may increase plasma levels of budesonide and fluticasone during concomitant dosing.<sup>1</sup> There is no known clinical effect.

## Tolerability

The inhaled corticosteroids are generally well tolerated.

Caution should be exercised when comparing adverse event data from different studies because of the differing patient populations, study methodologies, outcome measures in the study designs, methods of collecting patient complaints, the duration of the trials, and the level of suspicion of clinical investigators. These factors could cause wide variance in reported incidence and discontinuation rates.

- *Cough* – The incidence rate for cough in clinical trials appears similar for all oral inhaled corticosteroids (see Table 5). In many RCTs, cough is considered an outcome marker of poor asthma control. Few studies report the drop-out rates for cough as an ADE. There are no head-to-head trials from which incidence rates can be obtained.

**Table 5: Incidence of cough with oral inhaled corticosteroids** (package insert information)

Drug	Incidence of Cough (Placebo)
Beclomethasone	9% (4%) <sup>17,18</sup>
Budesonide	6% (2%) <sup>19</sup>
Flunisolide	3-9% (NA) <sup>1</sup>
Fluticasone	(reported, % not specified) <sup>20</sup>
Triamcinolone	1-3% (NA)

- *Oral Candidiasis* – Oral candidiasis (OC) has been reported with all of the oral inhaled corticosteroids. Positive cultures for oral Candida may be found in up to 75% of patients, but clinical thrush occurs in only 4% to 13%. This clinically apparent infection may require treatment with anti-fungal agents or discontinuation of the drug.<sup>1</sup> The reported incidences of clinically apparent infection are: fluticasone (2-5%), flunisolide (3-9%), beclomethasone (>10%), budesonide (>10%), and triamcinolone (1-10%).<sup>1,21</sup> As discussed, caution should be exercised when comparing this data.
- *Voice abnormalities* – Hoarseness or other voice abnormalities have been reported with all of the oral inhaled corticosteroids.<sup>1</sup> These symptoms are thought to be due to a local steroid myopathy of the vocal cords. The incidence is related to the total dose of inhaled steroid, but not the frequency of administration.<sup>22,23,24</sup> Symptoms subside when the inhaled steroid is withdrawn.<sup>25</sup>
- *Taste* – Flunisolide has been reported to have an extremely bitter taste. The incidence is reported as 10% in the manufacturer’s prescribing information.

## Efficacy

The FDA approved indications for the oral inhaled corticosteroids are listed in Table 6.

**Table 6: FDA-approved indications**

Generic Name	Trade Name	Asthma	Reduction of Oral steroid Dose
Beclomethasone	Vanceril, Beclovent	Yes	No
Beclomethasone	QVar	Yes	Yes
Budesonide	Pulmicort	Yes	Yes
Flunisolide	Aerobid	Yes	No
Fluticasone	Flovent	Yes	Yes
Triamcinolone	Azmacort	Yes	No

### 1. Efficacy of oral inhaled corticosteroids in the maintenance treatment of asthma

All oral inhaled corticosteroids are approved for the maintenance treatment of asthma.

Table 7 summarizes those comparative trials that were sufficiently powered to determine a statistical difference between the drugs studied. However, it is difficult to compare results across studies because of differing durations, study design, inclusion/exclusion criteria, and outcome measures. For instance, one cannot compare differences in FEV<sub>1</sub> or PEF<sub>R</sub> across studies if one of the studies was done in young children because young children have difficulty performing these tests. It is also problematic to compare symptom scores across studies. Symptom score instruments measure the patient's self-reported perceptions of symptoms over time. Wheezing, cough, shortness of breath, chest tightening, nocturnal awakenings, nocturnal cough, and fear of symptoms are typical measures seen on a symptom score instrument. The difficulty with cross-study comparison is that the researchers may have used different instruments, and the instruments may have differing degrees of validity. Despite these limitations, it appears that high potency oral inhaled corticosteroids are more efficacious than low potency for the maintenance treatment of asthma when given in comparable doses. This may be due to the fact that patients treated with high potency oral inhaled corticosteroids are more likely to receive the full dose of medication.

**Table 7: Oral Inhaled Corticosteroids in Patients with asthma**

Drug	Description of trial, systematic review or meta-analysis	Comments
Budesonide, beclomethasone <sup>26</sup>	RCT, parallel group, O. BUD v BEC. N=146. Outcome = FEV <sub>1</sub> ; (age range = 18 – 60yrs)	Budesonide 200 mcg/day significantly better than beclomethasone 400 mcg/day in improvement of FEV <sub>1</sub> . Non-significant for secondary measures (b-agonist use, nighttime awakenings, exacerbations)
Fluticasone, beclomethasone <sup>27</sup>	RCT, DB. N=274. FLT v BEC. Outcome = FEV <sub>1</sub> , SS, b-agonist use; (age range = 12-60 yrs)	Fluticasone 200 mcg/day significantly better than beclomethasone 400, 800 mcg/day in FEV <sub>1</sub> , b-agonist use. Fluticasone = beclomethasone in SS.
Fluticasone, beclomethasone <sup>28</sup>	RCT, DB. FLT v BEC. N=398, Outcome = FEV <sub>1</sub> , SS, b-agonist use.	Fluticasone 200 mcg/day = beclomethasone 400 mcg/day in FEV <sub>1</sub> . Fluticasone significantly better in SS, b-agonist use.
Flunisolide, beclomethasone <sup>29</sup>	RCT, SB, parallel group. N=99. Outcome= asthma exacerbations, SS.	Flunisolide 1000 mcg/day significantly better in reduction of exacerbations, improvement of symptom scores compared to beclomethasone 400 mcg/day.
Budesonide, beclomethasone <sup>30</sup>	RCT, DB, CO. n = 24. (age range = 4-14 yrs). Outcome = PEF <sub>R</sub> , FEV <sub>1</sub> .	PEFR, FEV <sub>1</sub> improved compared to placebo. Budesonide 200 mcg/day significantly (p< .01) improved morning PEF <sub>R</sub> 20% and evening PEF <sub>R</sub> 14% compared to improvements of 14% and 9% respectively with beclomethasone 200 mcg/day.
Fluticasone, beclomethasone <sup>31</sup>	RCT, DB. N= 398. (age range = 4-19 yrs) Outcome = PEF <sub>R</sub> , SS, plasma cortisol	Fluticasone 100 mcg/day improved PEF <sub>R</sub> significantly compared to beclomethasone 200 mcg/day; all other outcomes showed no significant difference.
Fluticasone, budesonide <sup>32</sup>	Open trial, PG. N=323. (age range = 4-11). Outcome = % PEF <sub>pred</sub> .	No significant difference in efficacy between fluticasone 200 mcg and budesonide 400 mcg.
Flunisolide, fluticasone <sup>33</sup>	Randomized, open, multicenter; n=328; 6 week. Age range = (18-63yr); Outcome=FEV <sub>1</sub> , PEF, SS.	No significant difference in FEV <sub>1</sub> , Fluticasone 500 mcg/day significantly better than flunisolide 2000 mcg/day with regard to PEF, SS.

Drug	Description of trial, systematic review or meta-analysis	Comments
Triamcinolone, fluticasone <sup>34</sup>	RCT, DB, PC. N=304; duration = 24 weeks; Outcome = FEV <sub>1</sub> , PEF, beta-agonist use.	Fluticasone was significantly better than triamcinolone in FEV <sub>1</sub> , PEF, and rescue use of beta-agonists.

RCT = Randomized controlled trial, SR = systematic review; FEV<sub>1</sub> = forced expiratory volume; PEF= peak expiratory flow rate; SS= symptom score; DB= double blind; PC= placebo controlled; O= open label; CO= crossover design; BUD=budesonide; BEC=beclomethasone; FLT=fluticasone; PEF = peak expiratory flow.

## 2. Efficacy of oral inhaled corticosteroids for reduction of oral systemic steroid dosage in chronic or acute asthma

The high potency oral inhaled corticosteroids are indicated for the reduction of oral systemic corticosteroid dosage in patients that require systemic corticosteroids for control of asthma. Other inhaled corticosteroids have been investigated for this use. QVar®, a brand of beclomethasone, is also FDA approved for this indication. No data are available comparing the relative efficacy of these products for this indication.

## 3. Efficacy of oral inhaled corticosteroids for other conditions

The inhaled corticosteroids are routinely used in chronic obstructive pulmonary disease. None of the inhaled corticosteroids are FDA-approved for this purpose. There are conflicting data on whether use of these agents appreciably affects the long-term decline associated with COPD.

Oral inhaled steroids have been studied in the emergency room setting as an alternative to systemic steroids. None of the inhaled corticosteroids are FDA approved for this purpose. However there is evidence in the literature that the high potency agents (budesonide and fluticasone) may be efficacious in lieu of oral steroids when given in this setting.<sup>35</sup> No data are available comparing the relative efficacy of these two products for this use.

## Other Factors

Other factors include patent expiration, provider preference, clinical practice guideline recommendations, dosing/administration, compliance/convenience issues, current usage/formulary status, and the existence of blanket purchase agreements, incentive price agreements, or contracts.

**Table 8: Patent Expirations**

Generic Name	Trade Name	Generic Available	Manufacturer, Patent Expiration
Beclomethasone	Beclovent®, Vanceril®	No	Glaxo-Welcome, Schering; Dec 1999
Beclomethasone	QVar®	No	3 M Pharmaceuticals
Budesonide	Pulmicort®	No	Astra USA; Apr 2006
Flunisolide	Aerobid®	No	Rhone-Polenc Rorer; June 2007
Fluticasone	Flovent®	No	Glaxo-Welcome; Nov 2003
Triamcinolone	Azmacort®	No	Rhone-Polenc Rorer; Jan 2007

## Clinical Practice Guideline Recommendations

The National Heart Lung and Blood Institute, the DOD/VA Clinical Practice Guideline Working Group, and the British National Institute for Clinical Excellence have all published practice guidelines that address the treatment of childhood asthma. These guidelines suggest the use of early intervention with inhaled corticosteroids as the mainstay of preventive therapy in order to avoid progression to more severe disease with airway remodeling.<sup>13,36,37</sup> None of these guidelines specify a particular inhaled corticosteroid as being more preferable than others. These guidelines state that selection of the inhaler should be governed first by individual patient need and compliance factors, then by cost minimization.

The DOD/VA Clinical Practice Guideline for the Treatment of Asthma does not recommend any specific oral inhaled corticosteroid. The algorithm suggests a clinical trial with an intermediate dose of inhaled corticosteroid in all patients whose FEV<sub>1</sub>/FVC ratio is less than 0.7 (0.8 in children) and whose asthma symptoms do not improve with inhaled bronchodilators. A positive response to this trial confirms the diagnosis of asthma and allows the provider to move into the long-term management. The algorithm recommends that all patients greater than or equal to 6 years of age whose asthma is graded as mildly persistent or greater should be on a daily maintenance dose of oral inhaled corticosteroids.

**Provider Preference/Expert Opinion** – Most providers had no strong preferences among oral inhaled corticosteroids. Those expressing a preference most commonly mentioned fluticasone for high potency. Most providers preferred to have at least one high potency and one low potency agent available. No provider recommended that this class be closed, a few specifically recommended not closing it. Comments from providers follow:

"Need a low dose/low strength option (Azmacort) plus higher dose/potency (Flovent 110,220). To d/c Azmacort, would need to replace with Flovent 44 ucg; this might make the pediatricians very happy"

"Pulmicort turbuhaler is a great alternative for kids/adults who are unable to coordinate using a regular MDI. It is also the only one with FDA approval for QD use..."

"Aerobid could be deleted. Flovent has a better safety profile..."

"You need to consider the entire gamut of patients from mild to severe, and infancy to elderly. I am not sure that there are really 1 or 2, or even three that meet this criteria."

"I would consider pulmicort and at least the strongest flovent-220 (and 110) as high potency: one of these must be given with a spacer to have adequate delivery (flovent)--at the present time"

"Because of the variability of patient performance, it is only good practice in my opinion to offer both a powder and a mdi with spacer in this category of potent steroids."

"--flovent 44 is certainly an excellent low potency steroid inhaler. However, at the present time I still have some reluctance to give up azmacort--the main reason being that the delivery with spacer is assured because of the device."

"For infants and young children, one needs an MDI which could be combined with a mask/aerochamber--which azmacort cannot do."

"We currently have Azmacort, Flovent, and Aerobid. We dumped Vanceril when it came off of the BCF. I think a steroid is a steroid is a steroid (keeping in mind the high vs low potency of course). We support whatever you do."

"Inhaled steroids - Getting contracts for commonly used drugs without adding to BCF or closing the class would be most helpful"

"... are not in favor of restricting the class down to one or 2 agents, but could live with the "work-horse" idea. For lower potency, they like Vanceril or Azmacort. For higher potency, Flovent is most popular here."

"The input from our docs regarding closing classes is generally not to do it. Selecting two workhorses and leaving the class open provides MTFs with flexibility while still "promoting" the most cost-effective and efficacious agents. We would like to see spacers provided to each new patient....a price discount on these would be great"

"Most all categories listed below can be contracted (probably closed). I think you need 2 inhalers. We have Azmacort and Flovent. Workhorse and high potency"

## Dosing and Administration

Flunisolide, beclomethasone, and triamcinolone are currently available as metered dose inhalers (MDIs). Budesonide is available as a dry powder inhaler (DPI). Fluticasone is available in both MDI and DPI delivery systems. These delivery systems deliver different amounts of drug to the lungs depending on user technique, raising concerns about switching patients from one delivery system to the other.

The current dosing recommendations for each of the available products is presented in Table 9. While none of the oral corticosteroid inhalers are FDA labeled as once daily products, there are published studies that support the effectiveness of once daily dosing in all of the oral inhaled corticosteroids except triamcinolone.

**Table 9: Dosing** (according to package labeling)

Generic	Trade name	Dosage Strengths	Recommended Starting Dose	Maximum Dose	Comments
Beclomethasone	Vanceril, Beclovent	42 mcg, 84 mcg	<b>Adults:</b> 84 mcg mcg tid-qid <b>Children:</b> 42 mcg tid-qid	<b>Adults:</b> 840 mcg/d in 3-4 doses <b>Children:</b> 420 mcg/d in 3-4 does	Single afternoon dose found to be effective in mild to moderate asthma <sup>38</sup>
Budesonide	Pulmicort	200 mcg	<b>Adults:</b> 200 – 400 mcg bid <b>Children:</b> 200 mcg bid	<b>Adults:</b> 800 mcg bid <b>Children:</b> 400 mcg bid	Once daily dosing of 400, 800 mcg has been shown to be effective <sup>39</sup>
Flunisolide	Aerobid	250 mcg	<b>Adults:</b> 500 mcg bid <b>Children:</b> 500 mcg bid	<b>Adults:</b> 1000 mcg bid <b>Children:</b> 500 mcg bid	Effective in doses of 1000 mcg once daily <sup>40</sup>
Fluticasone	Flovent	44 mcg, 110 mcg, 220 mcg	88 – 220 mcg bid	440 - 880 mcg bid	Once daily dosing has been shown to be safe and effective up to 375 mcg <sup>41,42</sup>
Fluticasone DPI	Flovent Rotadisk	50 mcg, 100 mcg, 250 mcg	<b>Adults:</b> 100 – 250 mcg bid <b>Children:</b> 50 mcg bid	<b>Adults:</b> 500 – 1000 mcg bid <b>Children:</b> 100 mcg bid	No once daily studies with DPI
Triamcinolone	Azmacort	100 mcg	<b>Adults:</b> 800 mcg/d in 2-4 doses <b>Children:</b> 300 –800 mcg/d in 2-4 doses	<b>Adults:</b> 1600 mcg/d in 3-4 doses <b>Children:</b> 1200 mcg/d in 3-4 doses	No once daily studies

### Compliance/Convenience Issues

Because of their recommended use as maintenance agents, the effectiveness of oral inhaled corticosteroids is greatly influenced by compliance. The number of puffs per dose have been shown to affect patient compliance. The lower potency agents require more puffs per dose to yield the same effectiveness. A comparison of the number of puffs required for equipotent dosing is shown in Table 2.

An additional cost/convenience issue is the use of spacer devices. The literature provides overwhelming evidence that using a spacer device with oral corticosteroids can enhance effectiveness and minimize side effects.<sup>1,2,36,37</sup> Azmacort® has a compliance advantage because its spacer is built-in, requiring no additional purchases. However, the Azmacort spacer device is a relatively small volume and its effectiveness may be less than larger volume spacers. Prescribers report that larger volume spacers are more effective than small volume spacers, and at least one clinical trial confirmed that larger volumes resulted in a greater percentage of drug delivered to the pulmonary area.<sup>43</sup> Pulmicort Turbuhaler® and Flovent Rotadisk® are dry powder inhalers and do not require a spacer. Azmacort, Pulmicort, and Flovent Rotadisk may be less useful in young children who require a face mask for more effective inhaled corticosteroid delivery.

Other issues of concern include lack of tactile feedback with dry powder inhalers, and patient education factors. Significant patient education would be necessary if the class was closed and patients were required to switch from an MDI to a DPI.

Table 10 summarizes a variety of characteristics that distinguish these agents from one another.

**Table 10. Inhaled Corticosteroids Product Comparison**

All drugs indicated for maintenance therapy in asthma

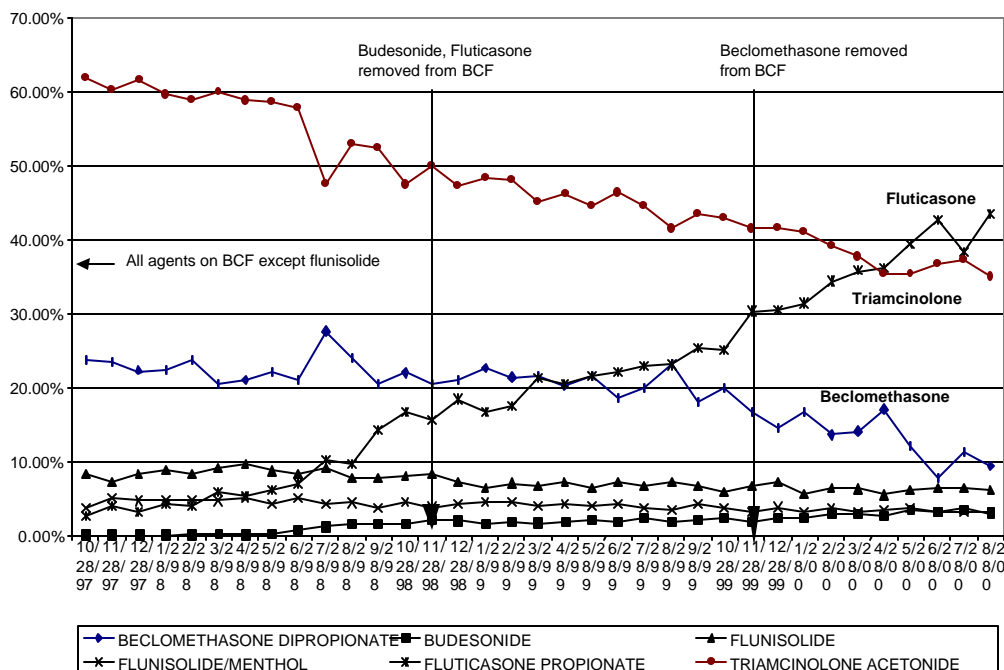
Drug	Formulation (availability & differences)	Safe in Infants	Use in Pediatrics	"Steroid-sparing" Labeling	Dosing Frequency	Spacer Required
Budesonide	DPI	Little or no evidence	Baran <sup>30</sup> (age 4-14 yr)	Yes	BID	No
Fluticasone	MDI, DPI Conde mi et al <sup>44</sup> DPI = MDI;	Little or no evidence	Rao <sup>13</sup> (age 5-10 yr); Williams <sup>32</sup> (age 4-11 yr); Gustaffson <sup>28</sup> (age 4-19 yr); Wolthers <sup>12</sup> (age 4-11 yr)	Yes	BID	MDI – Yes DPI – No
Beclomethasone	MDI, CFC Free MDI (Qvar®)	Liu <sup>45</sup> (neonates); Giep <sup>46</sup> (neonates); Huang <sup>47</sup> (age 6-36 mo); Yukse <sup>45</sup> (< 2 yr)	Huang <sup>47</sup> (age 6-36 mo) Baran <sup>30</sup> (age 4-14 yr)	QVar - Yes Vanceril - No Beclovent - No	Qvar - BID Vanceril - BID-TID Beclovent - BID-TID	Yes
Flunisolide	MDI	Little or no evidence		No	BID	Yes
Triamcinolone	MDI	Little or no evidence	Banov <sup>48</sup> (age 6-11 yr)	No	TID-QID	No (built-in)

All of the oral inhaled corticosteroids have been used in pediatric patients. Beclomethasone and fluticasone have the bulk of the clinical trial evidence for use in pediatrics. Only beclomethasone has clinical trials to support its use in neonates and very young infants. Some pulmonologists have suggested that DPI inhalers not be used in children under 5. Additionally, national guidelines recommend beclomethasone for young children requiring a mask-type spacer.

## Market Share

Figure 1 below shows the relative market share for the various products, determined from data obtained from the Uniformed Services Prescription Database (10/97-8/00).

**Figure 1 - Oral Inhaled Corticosteroid Market Share-Units Dispensed**



## Blanket Purchase Agreements/Incentive Agreements/Contracts for Oral inhaled corticosteroids

There are currently no DOD-wide blanket purchase agreements, incentive agreements, or contracts in effect for these agents.

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